The Genetic Risk of Kidney Disease in Type 2 Diabetes

Marcus G. Pezzolesi, PhD, MPH[a,b,*],
Andrzej S. Krolewski, MD, PhD[a,b]

KEYWORDS

• Type 2 diabetes • Diabetic nephropathy • Kidney disease • Genetic risk

KEY POINTS

- Evidence in favor a genetic basis for the susceptibility of diabetic nephropathy (DN) in type 2 diabetes (T2D) has provided a foundation for studies aimed at identifying the causal genes responsible for its development.
- During this period, strategies used to map genes for DN have been driven by our understanding of variation across our genome and the technologies available to interrogate it; as both have evolved, so to have our approaches.
- The advent of next-generation sequencing technology and increased interest in the search for rare variants has begun to swing the pendulum of these efforts toward studies of pedigrees.
- Family based approaches should greatly facilitate efforts to identify variants in genes that have a major effect on the risk of DN in T2D. To be successful, the ascertainment and comprehensive study of families with multiple affected members is critical.

INTRODUCTION

Diabetic nephropathy (DN) is a major late complication of diabetes that affects approximately 40% of all patients with diabetes and remains the leading cause of end-stage renal disease (ESRD) in the United States.[1–3] As the incidence of type 2 diabetes (T2D) continues to increase in the United States and across the globe, so to are the personal and societal burdens associated with this complication.

Investigations on the familial clustering of DN in T2D and the heritability of DN and its related traits provide compelling evidence that genetic factors contribute to its susceptibility and have motivated studies aimed at identifying the causal genes

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[a] Section on Genetics and Epidemiology, Research Division, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215, USA; [b] Department of Medicine, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
* Corresponding author. Section on Genetics and Epidemiology, Joslin Diabetes Center, Room 445C, One Joslin Place, Boston, MA 02215.
E-mail address: marcus.pezzolesi@joslin.harvard.edu

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responsible for its development. For more than 20 years, investigators have been working to identify the genes that underlie its susceptibility. During this period, advances in genomics have expanded our understanding of genetic variation across our genome and its contribution to disease and facilitated cutting-edge technologies that have revolutionized our ability to identify the genes that underlie these conditions.

In this review, we discuss the approaches used to identify DN susceptibility genes in T2D, including their key findings, and present our perspective on future studies in this field.

FAMILIAL CLUSTERING OF NEPHROPATHY AND ESTIMATES OF ITS HERITABILITY IN T2D

Evidence of familial aggregation supports the notion that genetic factors play a major role in the susceptibility of DN in T2D.[4–7] In the earliest investigation of familial clustering of DN among families with T2D, Pettitt and colleagues[4] examined the risk of proteinuria among 316 Pima Indian families with diabetes in 2 generations. In this study, the risk of proteinuria among offspring with diabetes with a parent with proteinuria was 1.8 times higher than that of offspring of parents with diabetes without proteinuria. The adjusted prevalence of proteinuria among individuals with one parent with diabetes with proteinuria was 23%, compared with only 14% among offspring with 2 parents with diabetes with normoalbuminuria. The prevalence of proteinuria among offspring with 2 parents with diabetes with proteinuria was even greater, with 46% of these individuals having this complication.

In 52 multigenerational African American families, Freedman and colleagues[5] found that 37% of the patients with T2D-induced ESRD had either a first-, second-, or third-degree relative with ESRD, compared with only 7% of T2D controls. Individuals with diabetes from these families with a relative with ESRD were at an eightfold increased risk of developing ESRD. Studies by Faronato and colleagues[6] and Canani and colleagues[7] similarly demonstrated that siblings with T2D of probands with DN from Caucasian families had 3 to 4 times the risk of developing microalbuminuria and macroalbuminuria compared with a sibling of normoalbuminuic probands. Faronato and colleagues[6] also confirmed a previous report by Gruden and colleagues[8] that demonstrated that the albumin excretion rate (AER) was increased in nondiabetic family members of patients with T2D.

To more precisely determine the relative contribution of genetic factors to DN in T2D, we and others have estimated the heritability (h^2; ie, the proportion of total variation of a trait caused by genetic effects) of its correlated traits (ie, urinary AER and estimated glomerular filtration rate [eGFR]) in families with T2D.[9–13] In 96 large multigenerational families that included 630 individuals with T2D and 639 individuals with normoglycemia enrolled in the Joslin Study on the Genetics of Type 2 Diabetes, Fogarty and colleagues[9] estimated that 27% of the variance in the albumin-to-creatinine ratio (ACR) was genetically determined among all family members regardless of their diabetes status. In analyses restricted to individuals with diabetes, this estimate increased slightly to 31% and, supporting previous reports of familial clustering of AER among nondiabetic family members, h^2 was estimated to be 0.20 in nondiabetic individuals from this collection.

A subsequent analysis of the Joslin Study on the Genetics of Type 2 Diabetes collection restricted to families with a middle age at the onset of T2D (46 ± 16 years) reported similar estimates of heritability with ACR, ranging from 0.20 in all family members to 0.39 in relatives without diabetes.[11] An important strength of the Joslin T2D family collection is that its members were ascertained for studies on the genetics of T2D, not kidney complications. As such, these estimates of heritability are unlikely